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The Global Burden of Ozone on Respiratory Mortality: No Clear Evidence for Association

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Anenberg et al. (2010) estimated the global burden of respiratory mortality attributable to long-term ozone exposure based on a single observational study by Jerrett et al. (2009). Because no other study has clearly demonstrated impacts of chronic ozone exposure on deaths from respiratory-related causes, we believe that reliance on the study by Jerrett et al. to establish causality and global impact is misplaced and that the conclusions of Anenberg et al. are likely unfounded.

Jerrett et al. (2009) carried out a follow-up analysis of the American Cancer Society (ACS) cohort. Other ACS studies reported no associations between long-term ozone exposure and cardiopulmonary mortality that are robust to model inclusion of co-pollutants (e.g., Krewski et al. 2000; Pope et al. 2002). In addition, other long-term studies of ozone-related respiratory or cardiopulmonary mortality did not report positive associations (Goodman 2010; Health Effects Institute 2009). Anenberg et al. (2010) suggested that long-term respiratory mortality is plausible because short-term ozone mortality has been documented, but inconsistent evidence for an association between short-term ozone exposure and respiratory mortality indicates that this relationship is not well established.

Jerrett et al. (2009) did not provide "clear" evidence of an association between long-term ozone exposure and respiratory mortality, as Anenberg et al. (2010) stated in their article. Jerrett et al. (2009) did not adequately control for potential confounding effects of particulate matter ≤ 2.5 μm in aerodynamic diameter ($PM_{2.5}$) for several reasons. Jerrett et al. (2009) used only 2 years of data for $PM_{2.5}$ (1999–2000) but ozone concentrations from 1977–2000. Although ozone and $PM_{2.5}$ levels decreased considerably from 1977 to 2000, they used higher ozone levels observed in the past but only the more recent $PM_{2.5}$ levels. Furthermore, their ozone metric focused on daily maximum hourly levels in the warm seasons, whereas they used annual average $PM_{2.5}$ concentrations. As noted by Jerrett et al. (2009), this approach likely increased the potential to observe an association between ozone and mortality and decreased the ability to observe potential $PM_{2.5}$ confounding of this association. In addition, confounding by other co-pollutants (e.g., sulfur dioxide), a clear issue in earlier ACS analyses (Krewski et al. 2000), was not examined. Accordingly, Jerrett et al. did not demonstrate an association between ozone and respiratory mortality that is independent of other co-pollutants.

Another aspect of the Jerrett et al. (2009) study that is inconsistent with an association between long-term ambient ozone exposure and respiratory mortality is the biologically implausible, inverse associations of ozone with cardiovascular and all-cause mortality. The magnitude of these associations is the same—although opposite in direction—as the risk estimate for respiratory mortality; thus, it is likely that associations of this magnitude are not indicative of a causal relationship.

It was inappropriate for Jerrett et al. (2009) to combine data across cities for a U.S. national risk estimate, given the known geographic heterogeneity of ozone-mortality findings (Goodman 2010). In addition, socioeconomic data (a potential confounder) was collected in 1982–1983 for the ACS study but never updated. For these reasons, the U.S. national risk estimate reported by Jerrett et al. (2009) should not be extrapolated globally.

The analysis by Anenberg et al. (2010) was based on an uncorroborated study that likely misinterpreted the findings regarding ozone effects. The utility of estimating the global burden of an effect based on a single study, for which no causal association has been established in other studies, is not apparent. Conclusions drawn from such an analysis should be interpreted with caution.

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References

Anenberg SC, Horowitz LW, Tong DQ, West JJ. 2010. An estimate of the global burden of anthropogenic ozone and fine particulate matter on premature human mortality using atmospheric modeling. Environ Health Perspect 118:1189–1195.

Goodman JE. 2010. Comments on US EPA's Proposed Reconsideration of the 2008 NAAQS for Ozone. Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OAR-2005-0172-11919 [accessed 8 March 2011].

Jerrett M, Burnett RT, Pope CA III, Ito K, Thurston G, Krewski D, et al. 2009. Long-term ozone exposure and mortality. N Engl J Med 360:1085–1095.

Katsouyanni K, Samet JM, Anderson HR, Atkinson R, Le Tertre A, Medina S, et al. 2009. Air Pollution and Health: A European and North American Approach (APHENA). Research Report 142. Boston:Health Effects Instititute.

Krewski D, Burnett RT, Goldberg MS, Hoover K, Siemiatycki J, Jerrett M, et al. 2000. Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality. Part II: Sensitivity Analyses. Boston:Health Effects Institute. Available: http://pubs.healtheffects.org/getfile.php?u=275 [accessed 10 March 2011].

Pope CA III, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, et al. 2002. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 287:1132–1141.

The Global Burden of Air Pollution on Mortality: Anenberg et al. Respond

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Prueitt and Goodman raise concerns about our use of chronic ozone mortality relative risk (RR) estimates from Jerrett et al. (2009) to estimate the global burden of outdoor ozone and fine particulate matter (< 2.5 μm in aerodynamic diameter; $PM_{2.5}$) on human mortality (Anenberg et al. 2010). We believe that our use of RR estimates from Jerrett et al. (2009) is justified and does not strongly affect our conclusions. Our goal of demonstrating the use of chemical transport models in estimating the global burden of outdoor air pollution on mortality is not affected by the choice of risk estimates. Further, using chronic RR estimates for ozone has only a minor effect on our mortality estimates, because the mortalities attributed to $PM_{2.5}$ are much greater than those for ozone.

We chose to use RR estimates from Jerrett et al. (2009) in our study (Anenberg et al. 2010) because they are consistent with the widely accepted RR estimates used for long-term $PM_{2.5}$ mortality (Krewski et al. 2009), as both are based on the American Cancer Society study cohort and capture delayed mortality effects (National Research Council 2008).

In response to particular criticisms, we note that while Jerrett et al. (2009) found the first significant positive association between chronic ozone exposure and mortality in a major cohort study, some previous smaller cohort studies have also found positive associations (National Research Council 2008). Biological plausibility for chronic ozone effects on respiratory mortality is evidenced by toxicology and human exposure studies that found that ozone affects airway inflammation, pulmonary function, and asthma induction and exacerbation (National Research Council 2008). Using earlier $PM_{2.5}$ data would be unlikely to affect confounding in the model, because using $PM_{2.5}$ data from 1979–1983 and 1999–2000 yields similar $PM_{2.5}$ mortality associations (e.g., Krewski et al. 2009). Jerrett et al. (2009) also found that socioeconomic data are not strong confounders and that

using more recent data is unlikely to change that conclusion (see Appendix of Jerrett et al. 2009). Finally, national risk estimates are more applicable globally than city-specific estimates because they include larger and more diverse populations.

However, because the evidence for chronic ozone mortality is more limited than the large body of evidence demonstrating mortality associations with short-term ozone exposure, we present here estimates of the global burden of ozone on mortality using RR estimates from Bell et al. (2004), a large multicity study of short-term ozone mortality. We estimated mortalities daily using the difference between preindustrial and present-day 8-hr maximum ozone, and sum mortalities over the 1-year simulation. We used the reported relationship for cardiopulmonary mortality and daily average ozone [0.64% (95% posterior interval, 0.31–0.98%) for a 10-ppb increase], and corrected to 8-hr ozone using the reported ratio between daily 8-hr and 24-hr average ozone associations with nonaccidental mortality.

Using these methods, we estimated 362,000 (95% confidence interval, 173,000–551,000) annual global premature cardiopulmonary deaths attributable to ozone, approximately 50% of the 700,000 premature deaths we calculated in our original study (Anenberg et al. 2010). Since estimated deaths due to $PM_{2.5}$ (3.7 million) are an order of magnitude larger, using a short-term rather than long-term RR estimate for ozone has only a minor effect on the overall global burden of disease due to outdoor air pollution. As RRs for chronic ozone mortality are not as strongly supported as those for $PM_{2.5}$, we expect that estimates of mortality burden will improve as research on chronic ozone exposure and mortality continues globally.

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References

Anenberg SC, Horowitz LW, Tong DQ, West JJ. 2010. An estimate of the global burden of anthropogenic ozone and fine particulate matter on premature human mortality using atmospheric modeling. Environ Health Perspect 118:1189–1195.

Bell ML, McDermott A, Zeger SL, Samet JM, Dominici F. 2004. Ozone and short-term mortality in 95 US urban communities, 1987-2000. JAMA 292:2372–2378.

Jerrett M, Burnett RT, Pope CA III, Ito K, Thurston G, Krewski D, et al. 2009. Long-term ozone exposure and mortality. N Engl J Med 360:1085–1095.

Krewski D, Jerrett M, Burnett RT, Ma R, Hughes E, Shi Y, et al. 2009. Extended Follow-up and Spatial Analysis of the American Cancer Society Study Linking Particulate Air Pollution and Mortality. Research Report 140. Boston:Health Effects Institute.

National Research Council, Committee on Estimating Mortality Risk Reduction Benefits from Decreasing Tropospheric Ozone Exposure. 2008. Estimating Mortality Risk Reduction and Economic Benefits from Controlling Ozone Air Pollution. Washington, DC:National Academies Press. Available: http://www.nap.edu/catalog.php?record_id=12198#toc [accessed 11 March 2011].

Influence of Selenium and Mercury on Age-Related Cataracts in the Brazilian Amazon

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In their article, Lemire et al. (2010) provided important data on the frequency of age-related cataracts among adults in the Brazilian Amazon and found a correlation between age-related cataracts and whole-blood total mercury (Hg) concentrations and selenium (Se) levels in plasma and whole blood. However, in the "Discussion" of their paper, they stated that they "observed no adverse effects although Se concentrations were very high, reaching 1,500 μg/L for [blood]-Se and 913 μg/L for [plasma]-Se" (Lemire et al. 2010). However, they did not mention the potential and substantial adverse health effects associated with a high body Se burden. There are potentially adverse consequences to Se body burden, such as hair loss (alopecia), tooth decay, nail changes, peripheral paresthesias, weakness, skin lesions, and diabetes (Hira et al. 2004; Nuttall 2006; Shearer 1975; Stranges et al. 2010; Sutter et al. 2008; Yang et al. 1983). It would be valuable to know what Se-related adverse effects were observed by Lemire et al. (2010). Most studies, taken together, suggest a possible attenuation of Hg toxicity, probably as insoluble form of Hg selenide (Clarkson 2002; International Programme on Chemical Safety 1990).

Selenium may be able to delay the onset of toxic effects in animal models exposed to methylmercury in the diet (Clarkson 2002; Ganther et al. 1972). However, the Hg–Se interaction may not have an equivalent effect in some animals. There is evidence that coadministration of methylmercury and Se may lead to an important synergistic effect (Heinz and Hoffman 1998). In studies of persons who have been co-exposed to Hg and Se, toxic effects of Se should be taken into account to discover the potential synergistic effect between Se and Hg.

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References

Clarkson TW. 2002. The three modern faces of mercury. Environ Health Perspect 110(suppl 1):11–23.

Ganther HE, Goudie C, Sunde ML, Kopecky MJ, Wagner P. 1972. Selenium: relation to decreased toxicity of methylmercury added to diets containing tuna. Science 175:1122–1124.

Heinz GH, Hoffman DJ. 1998. Methylmercury chloride and selenomethionine interactions on health and reproduction in mallards. Environ Toxicol Chem 17:139–145.

Hira CK, Partal K, Dhillon KS. 2004. Dietary selenium intake by men and women in high and low selenium areas of Punjab. Public Health Nutr 7:39–43.

International Programme on Chemical Safety. 1990. Methylmercury. Environmental Health Criteria 101. Geneva:International Programme on Chemical Safety, World Health Organization. Available: http://www.inchem.org/documents/ehc/ehc/ehc101.htm [accessed 2 March 2011].

Lemire M, Fillion M, Frenette B, Mayer A, Philibert A, Passos CJ, et al. 2010. Selenium and mercury in the Brazilian Amazon: opposing influences on age-related cataracts. Environ Health Perspect 118:1584–1589.

Nuttall KL. 2006. Evaluating selenium poisoning. Ann Clin Lab Sci 36:409–420.

Shearer TR. 1975. Developmental and postdevelopmental uptake of dietary organic and inorganic selenium into the molar teeth of rats. J Nutr 105:338–347.

Stranges S, Laclaustra M, Ji C, Cappuccio FP, Navas-Acien A, Ordovas JM, et al. 2010. **Higher selenium status is associated with adverse blood lipid profile in British adults.** J Nutr 140:81–87.

Sutter ME, Thomas JD, Brown J, Morgan B. 2008. Selenium toxicity: a case of selenosis caused by a nutritional supplement. Ann Intern Med 148:970–971.

Yang GQ, Wang SZ, Zhou RH, Sun SZ. 1983. Endemic selenium intoxication of humans in China. Am J Clin Nutr 37:872–881.

Influence of Selenium: Lemire et al. Respond

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We agree with the comments made by Minoia et al. in their letter. In this study population, we did evaluate the sentinel signs and symptoms of selenosis (Lemire M, Philibert A, Fillion M, Passos CJS, Guimarães JRD,